

72. (New) A unit dose formulation according to claim 71 wherein the agent is in admixture with a pharmaceutically acceptable carrier.--

REMARKS

I. Status of Claims

Claims 1-18 and 21-30 are pending in the instant case and stand variously rejected under 35 U.S.C. §112, first and second paragraphs. Claims 31-72 are new. The Applicants acknowledge with thanks the Examiner's rejoinder of Group I with Group III and rejoinder of Group II with Group IV after reconsideration of the original restriction requirement.

Applicants have amended claims 1, 10, 18, 21, 22, and 26-29. Attached hereto is a marked-up version of the changes made to the claims entitled "Version of Markings to Show Changes Made" (Appendix A). For the Examiner's convenience, applicants also have attached on Appendix B entitled "Claims Pending Upon Entry of Instant Amendment" which provides a clean copy of all the claims pending as of entry of the instant amendment.

It will be apparent from the remarks below that most of the amendments made to the pending claims merely adopt the Examiner's suggestions for placing the claims in condition for allowance. The suggestions have been adopted solely to expedite allowance, and not as an acquiescence to any rejection or objection. The amendments are discussed more fully below.

The Applicants have canceled claims 19 and 20 solely because the Patent Office has withdrawn them from consideration, as being directed to a non-elected invention. The Applicants reserve the right to pursue subject matter of any original claim (canceled or amended) in subsequent applications, such as continuing applications. Claim 9 was canceled in view of amendment to claim 1 in which the language the term "... operatively linked to a promoter to promote expression of the VEGF-C in cells of the blood vessel..." was added to claim 1.

The Examiner objected to claims 22-30 because these claims embraced non-elected (in addition to elected) subject matter. The amendments to restrict these claims to the elected invention are made solely to comply with Patent Office

restriction requirement practice and not in response to any rejection or in order to comply with any patentability requirement.

Applicants present new claims 31-72. These claims are fully supported by the specification as filed and the addition of these new claims does not constitute an introduction of new matter into the present application. Support for the new may generally be found throughout the specification, in particular, Applicants present herewith Appendix C containing a table which indicates exemplary support in the specification. Briefly, new claims 33 to 47 depend from independent claims 21 but are otherwise substantially similar to original claims 2 through 17 which depend from independent claim 1. New claim 48 is substantially similar to original claim 18 except that new claim 48 is directed to treatment using a vector comprising a polynucleotide encoding a VEGF-D polypeptide. Polynucleotides encoding a VEGF-D polypeptide are supported in the specification, for example, at page 21, lines 7-27 and in original claim 21. New claims 49-72 are supported by the specification as filed as indicated in attached Appendix C.

II. The Information Disclosure Statement should be considered.

The Examiner indicated that the information disclosure statement filed August 24, 2000 failed to comply with 37 C.F.R. §1.98(a)(2) and 37 C.F.R. §1.98(a)(1), alleging that copies of the documents cited in the PTO Form 1449 were not submitted with the information disclosure statement. The information disclosure statement was not considered. Applicants respectfully traverse the objection, because copies of all the cited documents were timely filed as part of the information disclosure statement. Attached herewith as Appendix D is a copy of a stamped, dated postcard received from the Patent and Trademark Office indicating receipt of the information disclosure statement "...w/25US, 15 FOR, 88OTH..." thereby establishing that Applicants submitted 25 U.S. patents, 15 foreign patent publications and 88 other references. Thus, the information disclosure statement was in full compliance with the requirements of 37 C.F.R. §§1.98(a)(1) and (a)(2), and should have been considered. However, since the documents appear to have been misplaced

at the Patent and Trademark Office, copies of these documents are being re-submitted herewith. Applicants respectfully request that the information disclosure statement filed August 24, 2000 be considered.

III. The Rejection of Claims under 35 U.S.C. §112, first paragraph should be withdrawn.

Claims 1-18 and 21-30 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. (See Office Action at pages 4-11.) Applicants respectfully traverse.

The Examiner rejected claims to a method of “preventing” restenosis and stenosis but indicated that claims to a method of “inhibiting” restenosis or stenosis are enabled by the specification. Apparently, it is the Examiner’s position that because gene therapy is a highly unpredictable art and because “prevention” allegedly is synonymous with complete amelioration or cure of restenosis/stenosis, then the claims to methods of preventing restenosis are not enabled by the specification. (Office Action at pages 4-7.) The Examiner acknowledged that:

“...The above rejections could be overcome by amending all claims to recite that stenosis or restenosis is inhibited rather than “prevented”...” (Official Action at page 11).

While Applicants respectfully disagree with the Examiner’s position that the term “prevention” means only complete prevention, in order to expedite prosecution and facilitate an early allowance of the claims of the instant application, the Applicants have adopted the Examiner’s suggestion. The claims have been amended herein such that the terms “prevent”, “preventing” and “prevention” have been replaced with the terms “inhibit”, “inhibiting” and “inhibition”, respectively. Applicants believe that those of skill in the art will understand that the term “inhibition” encompasses any amount of therapeutically beneficial effect and have always intended to pursue claims of such scope. The Examiner indicated at page 11

of the Official Action that such an amendment would obviate the grounds for the rejection. Applicants therefore request that the rejection be withdrawn.

The Examiner further rejected the claims because claims 1 and 21 did not recite a promoter, alleging that as such the claims encompass administering a gene without a promoter and the specification fails to teach that administering a polynucleotide encoding VEGF-C or VEGF-D without expression would be effective in treating and preventing restenosis. (Office Action at pages 7-8.) The Examiner indicated that the rejection would be overcome by reciting operable linkage to a promoter. (Office Action at page 11.) Applicants have adopted this suggestion and amended claims 1, 21, 22 and 26-29 to recite of a promoter linked to the polynucleotide. Applicants request that the rejection therefore be withdrawn as moot.

As a further basis for rejection the Examiner stated that claims 1-18 and 21 encompassed systemic delivery, and alleged that the specification only enables delivery of the polynucleotide to the location of the target cells to inhibit restenosis or stenosis. (Office Action at pages 8-10.) Applicants traverse the rejection. The specification, in the paragraph bridging pages 9 and 10, specifically contemplates administering using any medically-accepted means for introducing a therapeutic. Those of skill in the art know how to administer therapeutic agents by injection, oral ingestion, intranasal topical or numerous other routes of administration. In light of the fact that these routes of administration are contemplated in the specification, Examiner's position is incongruous with the enablement requirements of 35 U.S.C. §112, first paragraph.

Nevertheless, in an attempt to expedite prosecution, Applicants have amended claims 1 and 21 to recite that the administering is carried out "...locally at the site of said stenosis or restenosis..."¹ Applicants believe this amendment overcomes the rejection and request that the rejection be withdrawn.

Applicants believe the amendments and responses presented above remove the grounds for rejection of the claims based on 35 U.S.C. §112, first

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It will be appreciated that there is continual blood flow through blood vessels, and the recitation that administration is local to the site of treatment is not intended to imply that all of the therapeutic composition must remain at the focus of administration.

paragraph. Applicants request withdrawal of the rejection and reconsideration of the application in light of this response.

IV. Rejection of Claims under 35 U.S.C. §112, second paragraph should be withdrawn.

The Examiner rejected claims 1-17 and 21 under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. It was the Examiner's position that claims 1 and 21 were incomplete because it was unclear how administration without expression correlates to a treatment of a subject to prevent stenosis or restenosis of a blood vessel. To clarify the claims, Applicants have amended claims 1 and 18 to positively recite "...wherein expression of said VEGF-C in said blood vessel inhibits..." and 21 to positively recite "...wherein expression of said VEGF-D in said blood vessel inhibits..." stenosis or restenosis. This amendment overcomes the rejection and places the claims in condition for allowance.

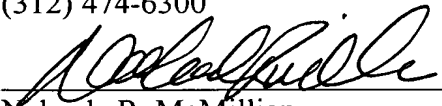
V. Conclusion

Applicants believe all the claims are now in a condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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APPENDIX A

Version of markings to show changes made

1. (Once Amended) A method of treating a mammalian subject to ~~prevent~~ inhibit stenosis or restenosis of a blood vessel, comprising the step of:
administering to a mammalian subject in need of treatment to ~~prevent~~ inhibit stenosis or restenosis of a blood vessel a composition comprising a polynucleotide, wherein said composition is administered locally at the site in need of treatment to inhibit stenosis or restenosis,
wherein said polynucleotide ~~comprising~~ encodes a nucleotide sequence that encodes a vascular endothelial growth factor C (VEGF-C) polypeptide operatively linked to a promoter to promote expression of the VEGF-C polypeptide in cells of the blood vessel, and thereby preventing
wherein expression of said VEGF-C polypeptide in said blood vessel cells inhibits stenosis or restenosis of said blood vessel.

9. CANCELED

10. (Amended) A method according to claim 9 1 wherein the polynucleotide further comprises a polyadenylation sequence operably connected to the sequence that encodes the VEGF-C polypeptide.

13. (Amended) A method according to claim 12 wherein said vector comprises a replication-deficient adenovirus, said adenovirus comprising the polynucleotide operably connected to a the promoter and flanked by adenoviral polynucleotide sequences.

18. (Once Amended) A treatment to ~~prevent~~ inhibit stenosis or restenosis of a blood vessel in a human, comprising delivering a replication-deficient adenovirus vector to the vessel, said vector comprising a polynucleotide encoding a VEGF-C polypeptide, and further comprising a promoter sequence to promote expression of the VEGF-C polypeptide in cells of the blood vessel, ~~thereby preventing~~ wherein

expression of said VEGF-C polypeptide in said blood vessel cells inhibits stenosis or restenosis of the blood vessel.

19. CANCELED

20. CANCELED

21.(Once Amended) A method of treating a mammalian subject to ~~prevent~~ inhibit stenosis or restenosis of a blood vessel, comprising the step of:

administering to a mammalian subject in need of treatment to ~~prevent~~ inhibit stenosis or restenosis of a blood vessel a composition locally at a site in need of treatment to inhibit stenosis or restenosis, said composition comprising ~~an anti-restenosis agent selected from the group consisting of Vascular Endothelial Growth Factor D (VEGF-D) polynucleotides and polypeptides, a polynucleotide comprising a nucleotide sequence that encodes a vascular endothelial growth factor D (VEGF-D) polypeptide operatively linked to a promoter to promote expression of the VEGF-D polypeptide in cells of the blood vessel, thereby preventing wherein expression of said VEGF-D polypeptide in said blood vessel cells inhibits~~ stenosis or restenosis of said blood vessel.

22. (Once Amended) [In] An improvement in a medical device designed to contact a surface of a blood vessel in the course of surgery to treat stenosis of the blood vessel, said improvement comprising integrating into the device a composition effective to prevent restenosis, said composition comprising at least one anti-restenosis agent selected from the group consisting of a VEGF-C polynucleotide operatively linked to a promoter that promotes expression of VEGF-C in cells of blood vessels, a VEGF-C polypeptide, and a VEGF-D polynucleotide operatively linked to a promoter that promotes expression of VEGF-D in cells of blood vessels; and a VEGF-D polypeptide.

26. (Once Amended) A medical device comprising an endovascular stent having an outer surface for contacting a surface of a blood vessel, and a composition on said surface, said composition comprising at least one anti-restenosis agent selected from the group consisting of a VEGF-C polynucleotide operatively linked to a promoter that promotes expression of VEGF-C polypeptide in cells of blood vessels; ~~a VEGF-C polypeptide;~~ and a VEGF-D polynucleotide operatively linked to a promoter that promotes expression of VEGF-D polypeptide in cells of blood vessels; ~~and a VEGF-D polypeptide.~~

27. (Once Amended) A medical device comprising a catheter having an outer surface for contacting a surface of a blood vessel, and a composition on said surface, said composition comprising at least one member selected from the group consisting of a VEGF-C polynucleotide operatively linked to a promoter that promotes expression of VEGF-C polypeptide in cells of blood vessels; ~~a VEGF-C polypeptide;~~ and a VEGF-D polynucleotide operatively linked to a promoter that promotes expression of VEGF-D polypeptide in cells of blood vessels; ~~and a VEGF-D polypeptide.~~

28. (Once Amended) A medical device comprising a balloon catheter having a void for holding a therapeutic agent for delivery to the interior of a blood vessel, and a composition contained in the void, the composition comprising at least one anti-restenosis agent selected from the group consisting of a VEGF-C polynucleotide operatively linked to a promoter that promotes expression of VEGF-C polypeptide in cells of blood vessels; ~~a VEGF-C polypeptide;~~ and a VEGF-D polynucleotide operatively linked to a promoter that promotes expression of VEGF-C polypeptide in cells of blood vessels; ~~and a VEGF-D polypeptide.~~

29. (Once Amended) A kit for treating restenosis comprising a container holding at least one anti-restenosis agent selected from the group consisting of a VEGF-C polynucleotide operatively linked to a promoter that promotes expression of VEGF-C polypeptide in cells of blood vessels; ~~a VEGF-C polypeptide;~~ ~~a VEGF-D~~

polynucleotide operatively linked to a promoter that promotes expression of VEGF-D polypeptide in cells of blood vessels, and a VEGF-D polypeptide; and a label attached to or packaged with the container, the label describing use of the ~~compound~~ agent for ~~prevention~~ inhibition of restenosis of a blood vessel.

Please add the following new claims:

--31. (New) A kit according to claim 30, further comprising a carrier substance for delivery of the agent to the luminal wall of a vessel.

32. (New) A kit according to claim 31, wherein the carrier is selected from the group consisting of a hydrogel polymer and microparticle polymers.

33. (New) A method according to claim 21 wherein said mammalian subject is human.

34. (New) A method according to claim 33 wherein said VEGF-D polypeptide comprises a mammalian VEGF-D.

35. (New) A method according to claim 33 wherein said VEGF-D polypeptide comprises a human VEGF-D.

36. (New) A method according to claim 33 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion consisting of positions 93-201 of SEQ ID NO: 4.

37. (New) A method according to claim 36 wherein said polynucleotide further comprises a nucleotide sequence encoding a secretory signal peptide, and wherein the sequence encoding the secretory signal peptide is connected in-frame with the sequence that encodes the VEGF-D polypeptide.

38. (New) A method according to claim 33 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion comprising positions 93-201 of SEQ ID NO: 4, wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 1-92 of SEQ ID NO: 4.

39. (New) A method according to claim 33 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion comprising positions 93-201 of SEQ ID NO: 4, wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 202-354 of SEQ ID NO: 4.

40. (New) A method according to claim 21 wherein the polynucleotide further comprises a polyadenylation sequence operably connected to the sequence that encodes the VEGF-D polypeptide.

41. (New) A method according to claim 33 wherein the composition further comprises a pharmaceutically acceptable carrier.

42. (New) A method according to claim 33 wherein the composition comprises a gene therapy vector, said gene therapy vector comprising said polynucleotide.

43. (New) A method according to claim 42 wherein said vector comprises a replication-deficient adenovirus, said adenovirus comprising the polynucleotide operably connected to the promoter and flanked by adenoviral polynucleotide sequences.

44. (New) A method according to claim 33 wherein said administering comprises at least one intravascular injection of said composition.

45. (New) A method according to claim 33 wherein said administering comprises a catheter-mediated transfer of said composition into a blood vessel of the mammalian subject.

46. (New) A method according to claim 45 wherein said catheter-mediated gene transfer comprises introducing a catheter into a coronary artery of the mammalian subject, and releasing the composition into the coronary artery.

47. (New) A method according to claim 33 wherein said administering is conducted in said human concurrently with a percutaneous transluminal coronary angioplasty.

48. (New) A treatment to inhibit stenosis or restenosis of a blood vessel in a human, comprising delivering a replication-deficient adenovirus vector to the vessel, said vector comprising a polynucleotide encoding a VEGF-D polypeptide, and further comprising a promoter sequence to promote expression of the VEGF-D polypeptide in cells of the blood vessel, wherein expression of said VEGF-D polypeptide in said blood vessel cells inhibits stenosis or restenosis of the blood vessel.

49. (New) A method of treating a mammalian subject to inhibit restenosis of a blood vessel, comprising the step of:

identifying a mammalian subject that has been or will be treated for a stenosed blood vessel; and

administering to the mammalian subject at the site of the stenosed blood vessel a composition comprising a polynucleotide, said polynucleotide comprising a nucleotide sequence that encodes a vascular endothelial growth factor C (VEGF-C) polypeptide or a vascular endothelial growth factor D (VEGF-D) polypeptide,

wherein the polynucleotide includes a promoter sequence operably linked to the encoding sequence to promote expression of the polypeptide in cells of the blood vessel, and

wherein expression of the VEGF-C or VEGF-D polypeptide inhibits restenosis of said blood vessel.

50. (New) A method according to claim 49 wherein said mammalian subject is human.

51. (New) A method according to claim 49 wherein the blood vessel is a coronary artery, and the administering is performed concurrently with percutaneous transluminal coronary angioplasty to treat the stenosed blood vessel.

52. (New) A method according to claim 49 wherein said polynucleotide comprises a nucleotide sequence encoding a mammalian VEGF-C polypeptide.

53. (New) A method according to claim 49 wherein said polynucleotide comprises a nucleotide sequence encoding a human VEGF-C polypeptide.

54. (New) A method according to claim 53 wherein said VEGF-C polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 2, said continuous portion having, as its amino terminus, an amino acid selected from the group consisting of positions 30-131 of SEQ ID NO: 2, and having, as its carboxyl terminus, an amino acid selected from the group consisting of positions 211 to 419 of SEQ ID NO: 2.

55. (New) A method according to claim 54 wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 228-419 of SEQ ID NO: 2.

56. (New) A method according to claim 55 wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 32-102 of SEQ ID NO: 2.

57. (New) A method according to claim 49 wherein said polynucleotide further comprises a nucleotide sequence encoding a secretory signal peptide, and

wherein the sequence encoding the secretory signal peptide is connected in-frame with the sequence that encodes the VEGF-C or VEGF-D polypeptide.

58. (New) A method according to claim 57 wherein the polynucleotide further comprises a polyadenylation sequence operably connected to the sequence that encodes the VEGF-C or VEGF-D polypeptide.

59. (New) A method according to claim 49 wherein said polynucleotide comprises a nucleotide sequence encoding a mammalian VEGF-D polypeptide.

60. (New) A method according to claim 59 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion consisting of positions 93-201 of SEQ ID NO: 4.

61. (New) A method according to claim 59 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion comprising positions 93-201 of SEQ ID NO: 4, wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 1-92 of SEQ ID NO: 4.

62. (New) A method according to claim 59 A method according to claim 33 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion comprising positions 93-201 of SEQ ID NO: 4, wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 202-354 of SEQ ID NO: 4.

63. (New) A method according to claim 49 wherein the composition comprises a gene therapy vector, said gene therapy vector comprising said polynucleotide.

64. (New) A method according to claim 63 wherein said vector comprises a replication-deficient adenovirus, said adenovirus comprising the polynucleotide flanked by adenoviral polynucleotide sequences.

65. (New) A method according to claim 49 wherein the composition further comprises a pharmaceutically acceptable carrier.

66. (New) A method according to claim 49 wherein said administering comprises at least one intravascular injection of said composition at the site of the stenosed blood vessel.

67. (New) A method according to claim 49 wherein said administering comprises a catheter-mediated transfer of said composition to the site of the stenosed blood vessel.

68. (New) A method according to claim 49 wherein said catheter-mediated gene transfer comprises introducing a catheter into a coronary artery of the mammalian subject, and releasing the composition into the coronary artery.

69. (New) A method according to claim 49 wherein said administering comprises implanting an intravascular stent in said mammalian subject at the site of the stenosed blood vessel, and wherein the stent is coated or impregnated with the composition.

70. (New) An extravascular collar designed to contact a surface of a blood vessel in the course of surgery to treat stenosis of the blood vessel, the collar comprising an outer wall shaped to surround the outer surface of a blood vessel, wherein the wall encloses a space containing a composition comprising a polynucleotide that comprises a nucleotide sequence encoding a VEGF-C polypeptide or a VEGF-D polypeptide, and wherein the polynucleotide further comprises a promoter to promote expression of the polypeptide in mammalian cells.

71. (New) A unit dosage formulation comprising a polynucleotide that comprises a promoter for promoting expression of a polypeptide in mammalian cells operably linked to a nucleotide sequence encoding a VEGF-C polypeptide or a VEGF-D polypeptide, packaged in a container, wherein the container includes a label containing an indication to use the formulation to treat restenosis.

72. (New) A unit dose formulation according to claim 71 wherein the agent is in admixture with a pharmaceutically acceptable carrier.--

APPENDIX B

Claims Pending Upon Entry of Instant Amendment

1. (Once Amended) A method of treating a mammalian subject to inhibit stenosis or restenosis of a blood vessel, comprising the step of:

administering to a mammalian subject in need of treatment to inhibit stenosis or restenosis of a blood vessel a composition comprising a polynucleotide,

wherein said composition is administered locally at the site in need of treatment to inhibit stenosis or restenosis,

wherein said polynucleotide comprises a nucleotide sequence that encodes a vascular endothelial growth factor C (VEGF-C) polypeptide operatively linked to a promoter to promote expression of the VEGF-C polypeptide in cells of the blood vessel, and

wherein expression of said VEGF-C polypeptide in said blood vessel cells inhibits stenosis or restenosis of said blood vessel.

2. A method according to claim 1 wherein said mammalian subject is human.

3. A method according to claim 2 wherein said VEGF-C polypeptide comprises a mammalian VEGF-C.

4. A method according to claim 2 wherein said VEGF-C polypeptide comprises a human VEGF-C.

5. A method according to claim 2 wherein said VEGF-C polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 2, said continuous portion having, as its amino terminus, an amino acid selected from the group consisting of positions 30-131 of SEQ ID NO: 2, and having, as its carboxyl terminus, an amino acid selected from the group consisting of positions 211 to 419 of SEQ ID NO: 2.

6. A method according to claim 5 wherein said polynucleotide further comprises a nucleotide sequence encoding a secretory signal peptide, and wherein the sequence encoding the secretory signal peptide is connected in-frame with the sequence that encodes the VEGF-C polypeptide.

7. A method according to claim 6 wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 228-419 of SEQ ID NO: 2.

8. A method according to claim 7 wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 32-102 of SEQ ID NO: 2.

10. (Amended) A method according to claim 1 wherein the polynucleotide further comprises a polyadenylation sequence operably connected to the sequence that encodes the VEGF-C polypeptide.

11. A method according to claim 2 wherein the composition further comprises a pharmaceutically acceptable carrier.

12. A method according to claim 2 wherein the composition comprises a gene therapy vector, said gene therapy vector comprising said polynucleotide.

13. (Amended) A method according to claim 12 wherein said vector comprises a replication-deficient adenovirus, said adenovirus comprising the polynucleotide operably connected to the promoter and flanked by adenoviral polynucleotide sequences.

14. (Once Amended) A method according to claim 2 wherein said administering comprises at least one intravascular injection of said composition.

15. (Once Amended) A method according to claim 2 wherein said administering comprises a catheter-mediated transfer of said composition into a blood vessel of the mammalian subject.

16. A method according to claim 15 wherein said catheter-mediated gene transfer comprises introducing a catheter into a coronary artery of the mammalian subject, and releasing the composition into the coronary artery.

17. A method according to claim 2 wherein said administering is conducted in said human concurrently with a percutaneous transluminal coronary angioplasty.

18. (Once Amended) A treatment to inhibit stenosis or restenosis of a blood vessel in a human, comprising delivering a replication-deficient adenovirus vector to the vessel, said vector comprising a polynucleotide encoding a VEGF-C polypeptide, and further comprising a promoter sequence to promote expression of the VEGF-C polypeptide in cells of the blood vessel, wherein expression of said VEGF-C polypeptide in said blood vessel cells inhibits stenosis or restenosis of the blood vessel.

21.(Once Amended) A method of treating a mammalian subject to inhibit stenosis or restenosis of a blood vessel, comprising the step of:

administering to a mammalian subject in need of treatment to inhibit stenosis or restenosis of a blood vessel a composition locally at a site in need of treatment to inhibit stenosis or restenosis, said composition comprising a polynucleotide comprising a nucleotide sequence that encodes a vascular endothelial growth factor D (VEGF-D) polypeptide operatively linked to a promoter to promote expression of the VEGF-D polypeptide in cells of the blood vessel, wherein expression of said VEGF-D polypeptide in said blood vessel cells inhibits stenosis or restenosis of said blood vessel.

22. (Once Amended) An improvement in a medical device designed to contact a surface of a blood vessel in the course of surgery to treat stenosis of the blood vessel, improvement comprising integrating into the device a composition effective to prevent restenosis, said composition comprising at least one anti-restenosis agent selected from the group consisting of a VEGF-C polynucleotide operatively linked to a promoter that promotes expression of VEGF-C in cells of blood vessels, and a VEGF-D polynucleotide operatively linked to a promoter that promotes expression of VEGF-D in cells of blood vessels.

23. The improvement of claim 22, wherein the device is selected from the group consisting of intravascular stents, intravascular catheters, and combinations thereof.

24. The improvement of claim 22, wherein the device comprises an extravascular collar.

25. The improvement of claim 22, wherein the device comprises an elastomeric membrane adapted to cover a surface of an intravascular stent or catheter.

26. (Once Amended) A medical device comprising an endovascular stent having an outer surface for contacting a surface of a blood vessel, and a composition on said surface, said composition comprising at least one anti-restenosis agent selected from the group consisting of a VEGF-C polynucleotide operatively linked to a promoter that promotes expression of VEGF-C polypeptide in cells of blood vessels and a VEGF-D polynucleotide operatively linked to a promoter that promotes expression of VEGF-D polypeptide in cells of blood vessels.

27. (Once Amended) A medical device comprising a catheter having an outer surface for contacting a surface of a blood vessel, and a composition on said surface, said composition comprising at least one member selected from the group consisting of a VEGF-C polynucleotide operatively linked to a promoter that promotes

expression of VEGF-C polypeptide in cells of blood vessels and a VEGF-D polynucleotide operatively linked to a promoter that promotes expression of VEGF-D polypeptide in cells of blood vessels.

28. (Once Amended) A medical device comprising a balloon catheter having a void for holding a therapeutic agent for delivery to the interior of a blood vessel, and a composition contained in the void, the composition comprising at least one anti-restenosis agent selected from the group consisting of a VEGF-C polynucleotide operatively linked to a promoter that promotes expression of VEGF-C polypeptide in cells of blood vessels and a VEGF-D polynucleotide operatively linked to a promoter that promotes expression of VEGF-D polypeptide in cells of blood vessels.

29.(Once Amended) A kit for treating restenosis comprising a container holding at least one anti-restenosis agent selected from the group consisting of a VEGF-C polynucleotide operatively linked to a promoter that promotes expression of VEGF-C in cells of blood vessels and a VEGF-D polynucleotide operatively linked to a promoter that promotes expression of VEGF-D in cells of blood vessels; and a label attached to or packaged with the container, the label describing use of the agent for inhibition of restenosis of a blood vessel.

30. A kit according to claim 29, further comprising a medical device selected from the group consisting of: intravascular stents, intravascular catheters, extravascular collars, and membranes adapted to cover a surface of an intravascular stent or catheter.

31. (New) A kit according to claim 30, further comprising a carrier substance for delivery of the agent to the luminal wall of a vessel.

32. (New) A kit according to claim 31, wherein the carrier is selected from the group consisting of a hydrogel polymer and microparticle polymers.

33. (New) A method according to claim 21 wherein said mammalian subject is human.

34. (New) A method according to claim 33 wherein said VEGF-D polypeptide comprises a mammalian VEGF-D.

35. (New) A method according to claim 33 wherein said VEGF-D polypeptide comprises a human VEGF-D.

36. (New) A method according to claim 33 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion consisting of positions 93-201 of SEQ ID NO: 4.

37. (New) A method according to claim 36 wherein said polynucleotide further comprises a nucleotide sequence encoding a secretory signal peptide, and wherein the sequence encoding the secretory signal peptide is connected in-frame with the sequence that encodes the VEGF-D polypeptide.

38. (New) A method according to claim 33 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion comprising positions 93-201 of SEQ ID NO: 4, wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 1-92 of SEQ ID NO: 4.

39. (New) A method according to claim 33 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion comprising positions 93-201 of SEQ ID NO: 4, wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 202-354 of SEQ ID NO: 4.

40. (New) A method according to claim 21 wherein the polynucleotide further comprises a polyadenylation sequence operably connected to the sequence that encodes the VEGF-D polypeptide.

41. (New) A method according to claim 33 wherein the composition further comprises a pharmaceutically acceptable carrier.

42. (New) A method according to claim 33 wherein the composition comprises a gene therapy vector, said gene therapy vector comprising said polynucleotide.

43. (New) A method according to claim 42 wherein said vector comprises a replication-deficient adenovirus, said adenovirus comprising the polynucleotide operably connected to the promoter and flanked by adenoviral polynucleotide sequences.

44. (New) A method according to claim 33 wherein said administering comprises at least one intravascular injection of said composition.

45. (New) A method according to claim 33 wherein said administering comprises a catheter-mediated transfer of said composition into a blood vessel of the mammalian subject.

46. (New) A method according to claim 45 wherein said catheter-mediated gene transfer comprises introducing a catheter into a coronary artery of the mammalian subject, and releasing the composition into the coronary artery.

47. (New) A method according to claim 33 wherein said administering is conducted in said human concurrently with a percutaneous transluminal coronary angioplasty.

48. (New) A treatment to inhibit stenosis or restenosis of a blood vessel in a human, comprising delivering a replication-deficient adenovirus vector to the vessel, said vector comprising a polynucleotide encoding a VEGF-D polypeptide, and further comprising a promoter sequence to promote expression of the VEGF-D polypeptide in cells of the blood vessel, wherein expression of said VEGF-D polypeptide in said blood vessel cells inhibits stenosis or restenosis of the blood vessel.

49. (New) A method of treating a mammalian subject to inhibit restenosis of a blood vessel, comprising the step of:

identifying a mammalian subject that has been or will be treated for a stenosed blood vessel; and

administering to the mammalian subject at the site of the stenosed blood vessel a composition comprising a polynucleotide, said polynucleotide comprising a nucleotide sequence that encodes a vascular endothelial growth factor C (VEGF-C) polypeptide or a vascular endothelial growth factor D (VEGF-D) polypeptide,

wherein the polynucleotide includes a promoter sequence operably linked to the encoding sequence to promote expression of the polypeptide in cells of the blood vessel, and

wherein expression of the VEGF-C or VEGF-D polypeptide inhibits restenosis of said blood vessel.

50. (New) A method according to claim 49 wherein said mammalian subject is human.

51. (New) A method according to claim 49 wherein the blood vessel is a coronary artery, and the administering is performed concurrently with percutaneous transluminal coronary angioplasty to treat the stenosed blood vessel.

52. (New) A method according to claim 49 wherein said polynucleotide comprises a nucleotide sequence encoding a mammalian VEGF-C polypeptide.

53. (New) A method according to claim 49 wherein said polynucleotide comprises a nucleotide sequence encoding a human VEGF-C polypeptide.

54. (New) A method according to claim 53 wherein said VEGF-C polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 2, said continuous portion having, as its amino terminus, an amino acid selected from the group consisting of positions 30-131 of SEQ ID NO: 2, and having, as its carboxyl terminus, an amino acid selected from the group consisting of positions 211 to 419 of SEQ ID NO: 2.

55. (New) A method according to claim 54 wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 228-419 of SEQ ID NO: 2.

56. (New) A method according to claim 55 wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 32-102 of SEQ ID NO: 2.

57. (New) A method according to claim 49 wherein said polynucleotide further comprises a nucleotide sequence encoding a secretory signal peptide, and wherein the sequence encoding the secretory signal peptide is connected in-frame with the sequence that encodes the VEGF-C or VEGF-D polypeptide.

58. (New) A method according to claim 57 wherein the polynucleotide further comprises a polyadenylation sequence operably connected to the sequence that encodes the VEGF-C or VEGF-D polypeptide.

59. (New) A method according to claim 49 wherein said polynucleotide comprises a nucleotide sequence encoding a mammalian VEGF-D polypeptide.

60. (New) A method according to claim 59 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of

SEQ ID NO: 4, said continuous portion consisting of positions 93-201 of SEQ ID NO: 4.

61. (New) A method according to claim 59 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion comprising positions 93-201 of SEQ ID NO: 4, wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 1-92 of SEQ ID NO: 4.

62. (New) A method according to claim 59 A method according to claim 33 wherein said VEGF-D polypeptide comprises an amino acid sequence comprising a continuous portion of SEQ ID NO: 4, said continuous portion comprising positions 93-201 of SEQ ID NO: 4, wherein said polynucleotide lacks a nucleotide sequence encoding amino acids 202-354 of SEQ ID NO: 4.

63. (New) A method according to claim 49 wherein the composition comprises a gene therapy vector, said gene therapy vector comprising said polynucleotide.

64. (New) A method according to claim 63 wherein said vector comprises a replication-deficient adenovirus, said adenovirus comprising the polynucleotide flanked by adenoviral polynucleotide sequences.

65. (New) A method according to claim 49 wherein the composition further comprises a pharmaceutically acceptable carrier.

66. (New) A method according to claim 49 wherein said administering comprises at least one intravascular injection of said composition at the site of the stenosed blood vessel.

67. (New) A method according to claim 49 wherein said administering comprises a catheter-mediated transfer of said composition to the site of the stenosed blood vessel.

68. (New) A method according to claim 49 wherein said catheter-mediated gene transfer comprises introducing a catheter into a coronary artery of the mammalian subject, and releasing the composition into the coronary artery.

69. (New) A method according to claim 49 wherein said administering comprises implanting an intravascular stent in said mammalian subject at the site of the stenosed blood vessel, and wherein the stent is coated or impregnated with the composition.

70. (New) An extravascular collar designed to contact a surface of a blood vessel in the course of surgery to treat stenosis of the blood vessel, the collar comprising an outer wall shaped to surround the outer surface of a blood vessel, wherein the wall encloses a space containing a composition comprising a polynucleotide that comprises a nucleotide sequence encoding a VEGF-C polypeptide or a VEGF-D polypeptide, and wherein the polynucleotide further comprises a promoter to promote expression of the polypeptide in mammalian cells.

71. (New) A unit dosage formulation comprising a polynucleotide that comprises a promoter for promoting expression of a polypeptide in mammalian cells operably linked to a nucleotide sequence encoding a VEGF-C polypeptide or a VEGF-D polypeptide, packaged in a container, wherein the container includes a label containing an indication to use the formulation to treat restenosis.

72. (New) A unit dose formulation according to claim 71 wherein the agent is in admixture with a pharmaceutically acceptable carrier.

APPENDIX C

Table Showing Support for New Claims

New Claim Number	Support in the Specification (original claim and/or page, line number(s))
31	page 16 lines 15-29
32	page 16 lines 26-29
33	original claim 2
34	original claim 3; page 21 lines 7-27
35	original claim 4; page 21 lines 7-27
36	original claim 5; page 21, lines 23-25
37	original claim 6; page 21, lines 7-27
38	original claim 7; page 21, lines 21-25
39	original claim 8; page 21, lines 21-25
40	original claim 10
41	original claim 11
42	original claim 12
43	original claim 13
44	original claim 14
45	original claim 15
46	original claim 16
47	original claim 17
48	original claim 18; page 21 lines 7-27
49	original claim 1, original claim 21, 5 lines 9-16
50	original claim 2
51	page 4 line 23 through page 5 line 8
52	original claim 3
53	original claim 4
54	original claim 5

55 original claim 7
56 original claim 8
57 original claim 6
58 original claim 10
59 page 21, lines 23-25
60 original claim 5; page 21, lines 23-25
61 original claim 7; page 21, lines 21-25
62 original claim 8; page 21, lines 21-25
63 original claim 12
64 original claim 13
65 original claim 11
66 original claim 14
67 original claim 15
68 original claim 16
69 page 26, lines 12-14
70 page 12 line 3; page 15, line 6-11
71 page 16, line 22
72 original claim 11